The University of Chicago

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A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
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R. UNIV. BIBLIOTHEEK LEIDEN

THE EFFECT OF METALLIC HALIDES ON SOME GRIGNARD REACTIONS

INTRODUCTION

The marked effect exerted by small quantities of certain metal halides on the course of some Grignard reactions was first systematically investigated by Kharasch and his coworkers[1] in their work with benzophenone and isobutylmagnesium bromide. Although benzhydrol is the normal product of the reaction, a 92 per cent yield of benzopinacol is obtained when 2 mole per cent of manganous chloride is added to the Grignard before the ketone is dropped into the solution. Other halides such as ferric chloride and chromic chloride give smaller amounts of the pinacol; cuprous chloride does not alter the course of the normal reaction. Thus, metal halides may be arranged in series according to the amount of pinacol which they produce in the isobutylmagnesium bromide-benzophenone reaction. As will be shown later, this serial order varies with the pair of reagents used, but, in a great many Grignard reactions, a catalytic amount of at least one salt of the sort mentioned profoundly changes the character of the reaction. Because it was found that a similar reaction would not produce pinacol from acetone, it was concluded that "one-electron reduction" occurred only with those ketones which in the absence of metallic halides are reduced to secondary alcohols by Grignard reagents. This limitation has been removed by later work.

Karasch and Tawney[2] continued the investigation of the metallic halide effect; they worked with methylmagnesium bromide and the cyclic unsaturated ketone, isophorone. This compound, with pure methylmagnesium bromide, gives only the 1,2 addition product; but when the reaction is run in the presence of cuprous

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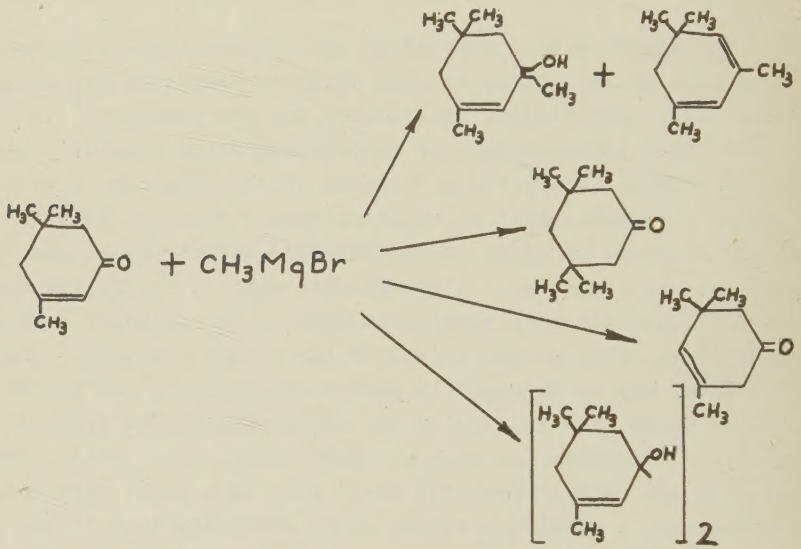
[1] Kharasch, Kleiger, Martin, and Mayo, J. Am. Chem. Soc., 63, 2305 (1941).

[2] Kharasch and Tawney, ibid., 63, 2308 (1941).

chloride, an 83 per cent yield of the 1,4 addition product can be isolated. Cobalt chloride so alters the reaction that isophorone pinacol is the main product. Ferric chloride acts in an unusual fashion; in its presence there is produced a large amount of an isomer of isophorone in which the double bond has shifted so that it is no longer conjugated with the carbonyl group. These effects are graphically represented as follows:



Benzalacetophenone, even though its double bond conjugated with the keto grouping is exocyclic, might be expected to behave very much like isophorone. Kharasch and Sayles[1] found however that the two compounds react somewhat differently. No metal halide has any great effect on the ratio of the 1,2 and 1,4 addition of methylmagnesium bromide to chalcone. Nevertheless, in the presence of cobaltous chloride the only reaction products are the two stereoisomeric forms of 1,4-dibenzoyl-2,3-diphenyl-butane[2] $(C_6H_5 \cdot CO \cdot CH_2 \cdot \underset{|}{C}H \cdot C_6H_5)_2$ compounds which might be called reduction dimers of chalcone.

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[1] Kharasch and Sayles, J. Am. Chem. Soc., 64, now in press.

[2] In other papers this compound has been called dibenzyl diacetophenone.

Ferric chloride and cuprous chloride give smaller quantities of these dimers, whereas manganous chloride has no effect on the reaction. In the presence of cobaltous chloride, phenylmagnesium bromide and chalcone give only two to five per cent of 1,4-dibenzoyl-2,3-diphenyl butane. Moreover, metallic halides do not markedly alter the interaction of ethylmagnesium bromide and chalcone; they slightly favor 1,2 addition. These facts demonstrate the importance of the particular Grignard reagent used in this type of reaction.

The investigations so far described have dealt with reactions of various Grignard reagents on carbonyl groups in the presence of metal halides. However, carbonyl compounds are not the only ones to undergo this new form of Grignard reaction. Kharasch and Fields[1] found that, in the presence of certain metal halides, aryl Grignard reagents, when treated with organic halides, give excellent yields of biaryls. The effectiveness of the metal chlorides descends from cobalt to nickel to iron. Manganous chloride has but a slight effect. Previous to this work, it had been necessary to use equimolar amounts of metallic salts in order to produce biaryl compounds from aryl Grignard reagents. Since, in the newly discovered reactions, only catalytic quantities of these metal halides are necessary, the following chain mechanism has been suggested:

$$C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl$$

$$2C_6H_5CoCl \longrightarrow C_6H_5\text{-}C_6H_5 + 2CoCl^{\bullet}$$

$$C_6H_5Br + CoCl^{\bullet} \longrightarrow CoClBr + C_6H_5^{\bullet}$$

$$x(C_6H_5^{\bullet}) \longrightarrow C_6H_6 + C_6H_5\text{-}C_6H_5$$

$$+C_6H_5\text{-}C_6H_4\text{-}C_6H_5, \text{ etc.}$$

Extended investigation of the action of Grignard reagents on halogen-containing compounds in the presence of metal salts has produced several useful results. Table 1 summarizes the findings of Kharasch and Sayles:[2]

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[1] Kharasch and Fields, J. Am. Chem. Soc., 63, 2316 (1941).

[2] Kharasch and Sayles, unpublished work.

TABLE 1

EFFECT OF COBALTOUS CHLORIDE[a] ON THE ADDITION OF HALOGEN CONTAINING COMPOUNDS TO GRIGNARD REAGENTS

Halogen Compound	Grignard Reagent	Per Cent Reaction	Addition of Halogen Cpd. to Grignard Reagent	Coupling of Halogen Cpd.	Unsaturation of Halogen Cpd.
$C_6H_5CH_2Cl$	C_4H_9MgBr	100	6	82	0
$(C_6H_5)_2CHCl$	C_6H_5MgBr	100	0	65[b]	0
$C_6H_5CH_2CH_2Br$	C_4H_9MgBr	70	0	49	34
$C_6H_5CHClCH_3$	C_6H_5MgBr	80	0	69[b]	0
$C_6H_5CH(CH_3)_2Cl$	C_4H_9MgBr	70	0	100	0

[a] Two mole per cent of the catalyst was employed.

[b] A large quantity of tar was found.

Table 1 shows that compounds containing a halogen attached to a phenylated carbon definitely tend to undergo dimerization. When the halogen is one atom away from the carbon holding the phenyl group, unsaturation is favored.

As an introduction to the work of the present paper it is necessary briefly to review previous work on the specific reactions to be discussed, namely, addition of Grignard reagents to unsaturated hydrocarbons, to certain ketones, and to some halogen containing compounds. Despite the fact that the addition of Grignard reagents to ethylenic linkages has been several times reported,[1] only one such report, that of Job[2] still stands unchallenged. Gilman[3] has investigated the action of different Grignard reagents

[1] Rupe and Bürgin, Ber., 43, 174 (1910); Lespieau, Bull. soc. chim., 29, 883 (1921); Staudinger, Kreis, Shilt, Helv. Chim. Acta, 5, 743 (1922).

[2] Job and Reich, Compt. rend., 179, 330 (1924).

[3] Gilman and Crawford, J. Am. Chem. Soc., 45, 554 (1923); Gilman and Shumaker, ibid., 47, 514 (1925); Gilman and Peterson, ibid., 48, 423 (1926); Gilman and McGlumphy, Rec. trav. chim., 47, 418 (1928); Gilman and Harris, ibid., 49, 762 (1930); Gilman, J. Am. Chem. Soc., 53, 2799 (1931).

on many ethylene and acetylene groups under varying conditions, but has found no instance of addition. Job worked with acetylene[1] and ethylene[2] itself. In his papers, however, the information regarding the amounts of products obtained is incomplete. Benzoic acid was obtained from the reaction of acetylene on phenylmagnesium bromide in the presence of small quantities of ferric chloride. The same Grignard reagent is stated to react with ethylene in the presence of nickel chloride to give benzene, styrene, ethane, and ethylbenzene. However, the amounts of these products are not stated.

Methylmagnesium bromide and phenylmagnesium bromide react with benzophenone to give only the addition products, diphenylmethylcarbinol[3] and triphenylcarbinol[4] respectively. These Grignard reagents thus differ from many others which reduce benzophenone to benzhydrol.[5] Cyclohexanone and methylmagnesium bromide, in the absence of any metallic halide, give 80 to 90 per cent of methyl cyclohexanol.[6] Isobutylmagnesium bromide reduces cyclohexanone to form large quantities of cyclohexanol; there is also a small yield of isobutyl cyclohexanol.[7] Phenylmagnesium bromide adds in the usual way to cyclohexanone; the product loses water to form 1-phenyl cyclohexene-1.[8]

No previous investigators have dealt explicitly with the action of Grignard reagents on 1-phenyl-3-chloro-propane and phenyl acetylene bromide, although one method of preparing the latter compound is:

$$C_6H_5C{\equiv}CMgBr + BrCN = C_6H_5C{\equiv}CBr + MgBrCN$$ [9]

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[1] Job and Champetier, Compt. rend., 189, 1089 (1929).

[2] Job and Champetier, Bull. soc. chim.[4], 47, 279 (1930); Job and Reich, Compt. rend., 179, 330 (1924).

[3] Blicke and Powers, J. Am. Chem. Soc., 51, 3378 (1929).

[4] Acree, Ber. 37, 625 (1904).

[5] Kharasch and Weinhouse, J. Org. Chem. 1, 209 (1936).

[6] Gutt, Ber. 40, 2069 (1907).

[7] Sabatier and Mailhe, Bull. soc. chim. [3], 33, 75 (1905).

[8] Ibid.

[9] Grignard and Courtot, Bull. soc. chim. [4], 17, 231 (1915).

There is an extensive literature concerning the reactions of cinnamyl chloride and bromide with Grignard reagents and with magnesium itself. As early as 1910 Rupe and Bürgin,[1] by treating cinnamyl chloride with magnesium, obtained a 10 per cent yield of dicinnamyl, together with a small amount of low boiling product and a larger quantity of high boiling material, supposedly 1,4-diphenyl-hexene-1. Later, Gilman and Harris[2] found that 75 per cent of the hydrocarbons formed in the reaction are high boiling. Of this fraction 9 per cent is dicinnamyl, 43 per cent 1,4-diphenyl hexadiene-1,5; the remainder is perhaps 3,4-diphenyl-hexadiene-1,5. Young, Ballou, and Nozaki[3] demonstrated that the low boiling product of the reaction contains 27 per cent propenyl benzene and 73 per cent allyl benzene. This fact indicates that an allylic rearrangement takes place during the formation of the Grignard reagent. The extent of this rearrangement, however, may not be as great as stated by Young et al., since his figures refer only to the low boiling material. The main portion of the Grignard reagent formed from cinnamyl chloride reacts immediately to form coupled products. Prevost[4] found an exchange reaction between ethylmagnesium bromide and cinnamyl bromide. The products of the reaction are:

TABLE 2

REACTION BETWEEN ETHYLMAGNESIUM BROMIDE AND CINNAMYL BROMIDE

Product	Yield (per cent)
CH_3CH_2Br	14
$C_6H_5CH_2CH{=}CH_2$	2.5
$C_6H_5CH{=}CHCH_3$	2.5
$C_6H_5CH{=}CHCH_2Et$	50
$C_6H_5{\cdot}CHEt{\cdot}CH{=}CH_3$	23
$C_6H_5CHCH{=}CH_2$ $\quad\quad\quad

These figures show that, after the cinnamyl bromide has taken the -MgBr from the ethylmagnesium bromide, a portion of the new Grignard reagent reacts with more cinnamyl bromide to form the coupled products.

DISCUSSION

The effect of metallic halides on the action of Grignard reagents on hydrocarbons containing an ethylenic bond.--In the hope that, with the aid of metallic halides, Grignard reagents could be added to ethylenic hydrocarbons, cyclonexene was treated with methylmagnesium bromide in the presence of cobaltous chloride. There was no reaction. Negative results were also obtained with styrene and methylmagnesium bromide, in the presence of cobaltous, ferric, and cuprous chlorides. When isoprene was used, varying amounts of high boiling material were obtained, but these may have been due to normal polymerization of the hydrocarbon. It is concluded that the product formed by the action of metallic halides upon the Grignard reagent is not sufficiently reactive to overcome the comparative lack of polarity in the unsaturated carbon to carbon linkage.

The effect of metallic halides on reactions between Grignard reagents and carbonyl compounds.--With carbonyl compounds, the results are decidedly different from reactions involving ethylenic substances; small amounts of metal salts completely change the normal course of the Grignard reaction. The aromatic ketone, benzophenone, and methylmagnesium bromide in the presence of various metallic halides give the following products:

TABLE 3

EFFECT OF METALLIC HALIDES ON THE REACTION OF BENZOPHENONE WITH METHYLMAGNESIUM BROMIDE

Metallic Halide or Metal Used (2 mole%)	Yield, % of Calculated Benzopinacol	Diphenylmethylcarbinol
None	0	95*
Mg	0	95
Cu_2Cl_2	0	93
$MnCl_2$	0	93
$FeCl_3$	65	21
$CoCl_2$	93	2

*Blicke and Powers, J. Am. Chem. Soc., 51, 3378 (1929).

These results indicate that metallic halides can exert a great effect on the normal addition of methylmagnesium bromide to benzophenone, since methylmagnesium bromide, in the absence of metallic halides, is devoid of reducing properties.[1]

It was of interest, therefore, to determine the effect of metallic halides in a reaction between benzophenone and a Grignard reagent which ordinarily acts as a reducing agent. Isobutylmagnesium bromide was selected for this purpose, because, without added metal halide, it reduces benzophenone to benzhydrol.[2] In the presence of cobaltous chloride, benzophenone yields 78 per cent of pinacol when it is treated with isobutylmagnesium bromide. This result combined with those of Kharasch and co-workers[3] is given in Table 4.

TABLE 4

EFFECT OF METALLIC HALIDES ON THE REACTION OF BENZOPHENONE WITH ISOBUTYLMAGNESIUM BROMIDE

Metallic Halide Used (1 to 2 mole %)	Yield, % of calculated	
	Benzopinacol	Benzhydrol
None	0	95
Cu_2Cl_2	0	91
$CrCl_3$	61	11
$FeCl_3$	71	..
$CoCl_2$	78	14
$MnCl_2$	92	2

Tables 3 and 4 show that, when the activity of a given metallic halide is under discussion, the type of Grignard reagent involved in the reaction must always be specified. For example, when isobutylmagnesium bromide (which ordinarily reduces benzophenone to benzhydrol in a two-electron reduction process) is treated with benzophenone in the presence of a metallic halide, manganous chloride is the halide most powerful in effecting a one-

[1] Blicke and Powers, J. Am. Chem. Soc., 51, 3378 (1929).

[2] Kharasch and Weinhouse, J. Org. Chem., 1, 209 (1936).

[3] Kharasch, Kleiger, Martin, and Mayo, op. cit.

electron reduction to benzopinacol. However, the reaction of methylmagnesium bromide (which ordinarily adds to benzophenone with no accompanying two-electron reduction) and benzophenone is completely unaffected by the addition of manganous chloride. Temperature, as well as the reducing power of the Grignard reagent, plays an important part in a Grignard reaction in the presence of a metal halide. At -40° benzophenone, isobutylmagnesium bromide, and cobaltous chloride give 78 per cent of benzhydrol, whereas at $+5^{\circ}$ the figures are, as given previously, 14 per cent.of benzhydrol and78 per cent of pinacol. This reversal may be due to the stabilization of the organocobalt subhalide, formed from the interaction of the Grignard reagent and cobaltous chloride, at the very low temperature. Whenever this active substance shows little tendency to decompose and initiate the chain reaction leading to one-electron reduction, the normal two-electron reduction outruns the benzopinacol formation. Phenylmagnesium bromide and benzophenone in the presence of cobaltous chloride yield at least 42 per cent of pinacol; no method has been found to separate the remaining mixture of pinacol and triphenylcarbinol into its components.

Since previous experiments had demonstrated the importance of the reducing power of the Grignard reagent in its reaction with a ketone in the presence of metallic halides, it seemed desirable to investigate the effect produced by using a ketone other than benzophenone. In general, aromatic ketones add Grignard reagents more slowly than do aliphatic ketones.[1] It seemed probable that an aliphatic ketone, such as cyclohexanone, would react with the Grignard reagent with such speed that the normal addition reaction would be unaffected by the addition of small quantities of metallic halides. This proved to be the case. No cyclohexyl pinacol was obtained from cyclohexanone and methylmagnesium bromide in the presence of cobaltous chloride, cobaltous iodide, ferric chloride or mixtures of these halides, although the temperature, the concentration of the reagents, and the order of their addition to the reaction mixture were varied. Phenylmagnesium bromide or isobutylmagnesium bromide and cyclohexanone also failed to give the pinacol in the presence of cobaltous chloride. However, a

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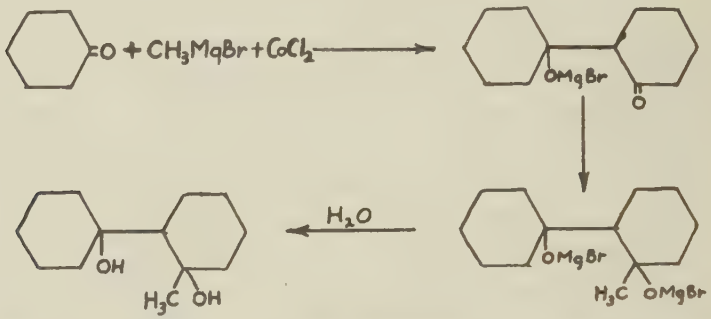
[1] Cooper, Ph.D. Dissertation, University of Chicago, 1937.

new compound (A) melting at 75° and having the formula $C_{13}H_{24}O_2$ was isolated from several reactions, especially the low temperature runs made in the presence of cobaltous chloride. The substance A may have been formed as follows:



It probably did not arise from hydration of an addition product of cyclohexylidene-cyclohexanone and methylmagnesium bromide, since these two compounds do not react in the presence of cobaltous chloride under the conditions here maintained.

The effect of metallic halides on reactions between Grignard reagents and halogen containing compounds.--Three representative compounds were selected for the study of the effect of metallic halides on Grignard reactions involving halogen containing compounds: 1) 1-phenyl-3-chloropropane: 2) cinnamyl chloride; 3) phenylacetylene bromide. The three substances possess a progressively greater unsaturation of the side chain from the chloropropane, $C_6H_5CH_2CH_2CH_2Cl$, to the allylic compound, $C_6H_5CH{=}CHCH_2Cl$, to the acetylene, $C_6H_5C{\equiv}CBr$. Thus, a study of their reactions furnishes an approach to the problem of the variance of the effect of metallic halides upon Grignard reactions involving organic halides.

The first compound investigated was 1-phenyl-3-chloropropane. In the control reaction between this compound and methylmagnesium bromide in the absence of metallic halide, halogen titration showed no increase of soluble halide, and all the organic halide was recovered. When cobaltous chloride was present, titration of the soluble halide showed a 100 per cent reaction. Little butyl benzene, the normal addition product, was formed. The methyl radical from the Grignard reagent was quantitatively converted to methane. The liquid product was a mixture of 20 per cent propyl benzene, 20 per cent allyl benzene, and 40 per cent propenyl ben-

zene. A small amount of material boiling in the range of diphenyl hexane was obtained, but since no crystalline nitration product of this material could be prepared, the substance may have been merely a polymer of allyl or propenyl benzene. These findings on 1-phenyl-3-chloropropane agree with previous observations in this laboratory;[1] the ease of dimerization of the free radical produced by removal of a halogen atom from an organic halide decreases in the following order: $C_6H_5\cdot > C_6H_5CH_2\cdot > C_6H_5CH_2CH_2\cdot$. The propyl benzene formed in this reaction did not arise from an exchange reaction between the Grignard reagent and the 1-phenyl-3-chloropropane since a halogen titration showed that all the halogen of the latter compound had been converted to ionized halogen.

Unlike 1-phenyl-3-chloropropane, the allylic compound, cinnamyl chloride, normally reacts with methylmagnesium bromide with ease. Here, too, metallic halides produce remarkable changes in the type of products obtained from the reaction.

TABLE 5

EFFECT OF METALLIC HALIDES ON THE REACTION BETWEEN CINNAMYL CHLORIDE AND METHYLMAGNESIUM BROMIDE[a]

Metallic Halide Used (5 Mole %)	Yield, % of Calculated		
	Addition	Coupling	
	$C_6H_5CH{=}CHCH_2CH_3$	1,6-diphenyl-hexadiene-1,5	1,4-diphenyl-hexadiene-1,5
None	89	1	5
Cu_2Cl_2	94	0	0
$FeCl_3$	77	6	9
$MnCl_2$	71	7	11
$CrCl_3$	19	20	44
$NiCl_3$	16	30	31
$CoCl_2$	12	30	40
$CoCl_2$[b]	54	20	14

[a]Cinnamyl chloride was added to a mixture of the metallic halide in methylmagnesium bromide at 5° C.

[b]Methylmagnesium bromide was added to the organic halide containing cobaltous chloride at room temperature.

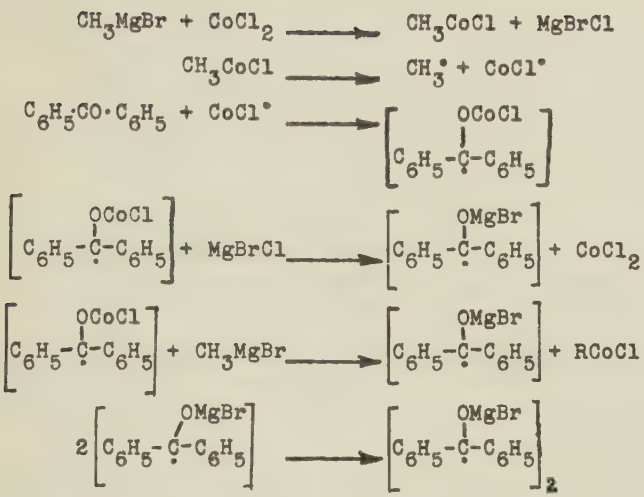
[1]Kharasch and Sayles, unpublished work.

Not more than a minute quantity of low boiling material (which may have been allyl or propenyl benzene) was detected in any one of the reactions. Therefore, very little exchange occurred, unless it was immediately followed by reaction between the newly formed Grignard reagent and the halogen compound formed in the exchange. The 100 per cent reaction, as shown by ionized halogen titration, also indicated that practically no exchange had occurred.

A word of explanation is necessary regarding the compound, phenylacetylene bromide, and its reaction with Grignard reagents. In contrast to the other substances studied in this investigation, phenylacetylene bromide shows a remarkable tendency to exchange its bromine atom for an -MgBr group with methylmagnesium bromide. This fact was demonstrated in two control reactions (without added metallic halide) between phenylacetylene bromide and methylmagnesium bromide. In reaction A, an almost quantitative yield of phenyl acetylene was obtained, and titration showed that no increase in ionized halogen had occurred. This indicates strongly that the exchange had taken place: $C_6H_5C{\equiv}CBr + CH_3MgBr \rightarrow C_6H_5C{\equiv}CMgBr + CH_3Br$. In reaction B, final proof of the exchange of the-MgBr group was obtained by treating the reaction mixture with carbon dioxide. Fifty-five per cent of the calculated amount of phenyl propiolic acid was isolated, together with 21 per cent of phenyl acetylene. However, when 5 mole per cent of cobaltous chloride was placed in the Grignard reagent and phenylacetylene bromide was added, 60 per cent of phenylmethyl acetylene was formed. The halogen titration indicated 100 per cent reaction, but relatively large amounts of tar were formed, perhaps by polymerization of the phenylmethyl acetylene.

Interpretation of the results.--The types of molecules which have been studied fall into three classes: (1) ketones, (2) halogen compounds such as 1-phenyl-3-chloropropane, and (3) bromacetylenes.

From the results which have been discussed, it is apparent that with ketones the significant effect of the addition of metallic halides to the Grignard reaction is a one-electron reduction of the ketone to a pinacol. For cobaltous chloride, methylmagnesium bromide, and benzophenone the suggested mechanism is:



It is evident that the stability of the intermediate organometallic compound, RCoCl, is of paramount importance, because its decomposition to form the subcobaltous halide propagates a chain. Little or no effect will be exerted on the normal reaction if the intermediate organometallic halide is stable. Moreover, little effect will be noted if the metallic subhalide itself, formed from the decomposition of RCoCl, is too unstable to propagate the chain. In support of these deductions, the experiments with isobutylmagnesium bromide and benzophenone may be cited. When benzophenone is treated at 5° with isobutylmagnesium bromide in the presence of cobaltous chloride, reduction to benzopinacol far outruns the normal two electron reduction to benzhydrol. However, at low temperatures the methylcobalt subchloride, CH_3CoCl, has little tendency to decompose to form $(CoCl)^{\cdot}$ and thus the normal reaction, two-electron reduction to benzhydrol, predominates. Another effect is seen in the case of cyclohexanone, in which the normal addition of the Grignard reagent to the ketone outruns the one-electron reduction favored by the addition of metallic halide to the reaction.

In the second class of compounds studied, that including 1-phenyl-3-chloropropane and cinnamylchloride, the action of the CH_3CoCl formed from the Grignard reagent and cobaltous chloride seems to be a removal of a halogen atom from the organic halide. Thus with cinnamyl chloride, methylmagnesium bromide, and cobaltous chloride, the reactions would be:

(1) $CH_3MgBr + CoCl_2 \longrightarrow CH_3CoCl + MgBrCl$

(2) $CH_3CoCl \longrightarrow CH_3^{\cdot} + CoCl^{\cdot}$

(3) $C_6H_5CH{=}CHCH_2Cl + CoCl^{\cdot} \longrightarrow C_6H_5CH{=}CHCH_2^{\cdot} + CoCl_2$

(4) $C_6H_5CH{=}CHCH_2^{\cdot} \longrightarrow C_6H_5\overset{\cdot}{C}HCH{=}CH_2$

(5) $2(C_6H_5CH{=}CHCH_2^{\cdot}) \longrightarrow (C_6H_5CH{=}CHCH_2{-})_2$

(6) $C_6H_5\overset{\cdot}{C}HCH{=}CH_2 + C_6H_5CH{=}CHCH_2^{\cdot} \longrightarrow C_6H_5\underset{\displaystyle CH_2CH{=}CHC_6H_5}{\overset{\displaystyle |}{C}}HCH{=}CH_2$

(7) $2(C_6H_5\overset{\cdot}{C}HCH{=}CH_2) \longrightarrow (C_6H_5\underset{\displaystyle |}{C}HCH{=}CH_2)_2$

(8) $C_6H_5CH{=}CHCH_2Cl + CH_3MgBr \longrightarrow C_6H_5CH{=}CHCH_2CH_3 + MgBrCl$

It is probable that the free radical, $C_6H_5\overset{\cdot}{C}HCH{=}CH_2$, when formed in reaction 4, immediately enters into reaction 6, because if there were an appreciable amount of these radicals in solution, they would couple as shown in reaction 7. None of this coupled product was detected in the experiments.

The course of the reaction of 1-phenyl-3-chloropropane with methylmagnesium bromide in the presence of cobaltous chloride is initially the same as that given for cinnamyl chloride. However, in contrast to the great tendency of the allylic radical to couple, the radical formed by removal of the chlorine atom from 1-phenyl-3-chloropropane tends to disproportionate. The formation of propenyl benzene, $C_6H_5CH{=}CHCH_3$, as well as allyl benzene, $C_6H_5CH_2CH{=}CH_2$, indicates that there is also a tendency for the radical to rearrange.

The third class of compounds, those which ordinarily exchange their halogen for the -MgBr grouping when treated with a Grignard reagent, includes phenylacetylene bromide. Here, as in the reactions previously mentioned, the function of the subhalide seems to be the removal of a halogen atom from the organic compound: $C_6H_5C{\equiv}CBr + CoCl^{\cdot} \rightarrow C_6H_5C{\equiv}C^{\cdot} + CoClBr$. The free radical produced

then can attack a molecule of methylmagnesium bromide or methylcobaltous chloride:

$$C_6H_5C{\equiv}C^{\cdot} + CH_3MgBr \longrightarrow C_6H_5C{\equiv}CCH_3 + MgBr^{\cdot}$$

$$C_6H_5C{\equiv}CBr + MgBr^{\cdot} \longrightarrow C_6H_5C{\equiv}C^{\cdot} + MgBr_2$$

$$C_6H_5C{\equiv}C^{\cdot} + CH_3CoCl \longrightarrow C_6H_5C{\equiv}CCH_3 + CoCl^{\cdot}$$

The chain is thus propagated with eventual formation of large quantities of phenylmethyl acetylene.

EXPERIMENTAL PART

Reagents.--Methyl bromide was obtained from the Dow Chemical Company. The magnesium employed in the first portion of the work was either sublimed or of radio grade. Mallinckrodt magnesium turnings were used in later work. Cuprous chloride was the usual anhydrous reagent; anhydrous manganous chloride was prepared by heating the hydrated salt in an oven for eight hours at 200°. Anhydrous ferric chloride was prepared from analytical grade iron wire and chlorine; anhydrous cobalt chloride, by heating the hydrated salt at 150° in vacuo. The chromic and nickel chlorides used were the usual anhydrous reagents.

Preparation of the Grignard reagent.--Methyl magnesium bromide was prepared in a three-necked flask equipped with mercury-sealed stirrer, reflux condenser, and inlet tube. In a representative experiment the magnesium was placed in the flask, and approximately 50 cc. of anhydrous ether was added. Dry methyl bromide was passed into the flask until the reaction started, at which time the remainder of the dry ether was added (sufficient to make a 2 molar solution of the Grignard). The methyl bromide was passed in at such a rate as to maintain a gentle reflux of the ether until the magnesium had been almost completely consumed. The Grignard reagent was then filtered through glass wool or glass cloth into a brown storage bottle. Phenyl-magnesium bromide was prepared in a similar manner from freshly distilled phenyl bromide.

Iso-butyl bromide was prepared by the method given in Or-

ganic Syntheses[1] and by the method of Tseng.[2] The alkyl halide was distilled through a 1.1 meter glass packed column. The boiling point was 91-91.2°, $n^{20}D$ 1.4360. From this halide the Grignard reagent was made as previously described.

Reaction of methylmagnesium bromide with benzophenone.--The Grignard reagent was filtered from the storage bottle (to remove any magnesium hydroxide which might have formed) into a graduated dropping funnel, and two five-milliliter aliquot portions were removed for titration. Usually 0.2 mole of Grignard reagent was placed in a three-necked flask equipped with a mercury-sealed stirrer, a thermometer, and a two-necked adapter fitted with a reflux condenser and dropping funnel. Two mole per cent of catalyst was added, and the resultant solution was stirred and cooled to 10°. One-tenth of a mole of benzophenone, dissolved in 50 g. of benzene, was placed in the dropping funnel and added at such a rate as to maintain the temperature of the solution between 10 and 20°. After the addition was complete the temperature was allowed to rise to that of the room. The solution was then refluxed gently for one to two hours and left overnight.

The magnesium alcoholate was decomposed by an ice-hydrochloric acid mixture, and the ethereal layer was separated. After the aqueous layer had been extracted several times with ether, the ethereal solutions were combined, washed with sodium carbonate solution, and with distilled water, and then dried over anhydrous sodium sulfate. The ether was removed on a steam-bath. The carbinol produced in the experiments with magnesium, cuprous chloride, and manganous chloride was crystallized from high-boiling ligroin. It melted at 79-81°.

In the cobaltous chloride experiments a solid residue remained after removal of the ether. The solid was leached with hot ligroin until half the substance had dissolved, and the remainder was then dissolved in hot 95 per cent alcohol. The two portions were fractionally crystallized. All fractions from the alcohol produced benzopinacol, 178-180° (dec.). The first fractions from ligroin produced benzopinacol, succeeding fractions

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[1] Organic Syntheses, XIII, p. 20.

[2] Tseng, J. Chinese Chem. Soc., 2, 57 (1934).

giving a mixture of benzopinacol and 1,2-addition product. The two compounds were separated by fractional crystallization from ligroin.

The product of the ferric chloride experiment was fractionally crystallized from 95 per cent alcohol. Pure pinacol crystallized at first. A mixture of pinacol and carbinol appeared in the last fractions. The substances were separated by fractional crystallization from ligroin.

In the experiment in which magnesium was added to the Grignard reagent, a red to red-violet coloration appeared during and shortly after the addition of the benzophenone. However, only diphenylmethylcarbinol was obtained, although a careful search was made for benzopinacol.

Reaction of benzophenone with isobutylmagnesium bromide.-- One-tenth of a mole of benzophenone was added to 0.17 moles of isobutylmagnesium bromide according to the usual procedure. Three mole per cent of cobaltous chloride were employed. The reaction mixture was refluxed for an hour and allowed to stand overnight; it was then filtered and decomposed with hydrochloric acid. When the product was worked up, the precipitate yielded 2.6 grams (14%) of benzhydrol, m. p. 64-66°; the filtrate gave 14 grams (78%) of benzopinacol, dec. pt. 180-183°. In another experimental run at plus 5° the reaction mixture was worked up immediately after it had been refluxed for an hour; the results were exactly the same as in the first experiment. An experiment carried out according to the usual procedure but at -40° C. gave 78 per cent of benzhydrol (m.p. 65-67°) and 7 per cent of benzopinacol (dec. pt. 182-183°).

Reaction of benzophenone with phenylmagnesium bromide.-- The usual technique and quantities of material were employed. After the reaction mixture had been steam distilled to remove diphenyl, the undistilled residue was taken up in benzene-ether and dried over sodium sulfate. The solvent was distilled off and the solid residue leached with 225 cc. of hot alcohol. When the residue was recrystallized from alcohol, it yielded 5.4 grams (31%) of benzopinacol. An attempt was made to separate the benzopinacol and triphenylcarbinol still remaining in the alcohol solution by taking advantage of the different solubilities of these substances in ether and in benzene-ligroin mixtures. However, these efforts met with no success. Repeated fractional crystallization from

ethyl alcohol gave an additional 1.5 grams of benzopinacol; but systematic recrystallization effected no further separation. The reduction of triphenylcarbinol to triphenylmethane[1] by use of formic acid failed. Ten grams of the carbonol-pinacol mixture were heated six minutes with 20 grams of aniline and 50 grams of acetic acid; the mixture was then poured into water.[2] Recrystallization (from alcohol) of the solid precipitate gave an additional 0.5 grams of pinacol, bringing the total pinacol recovery to 7.6 grams (42%). Succeeding fractions were so impure that the components could not be separated.

Reaction of methylmagnesium bromide with cyclohexanone.--The cyclohexanone was purified by storage over calcium chloride for several days, and then distilled at reduced pressure. (Boiling point 43.5° at 11 mm.; $n^{20}D = 1.4500$.) The apparatus and procedure used in the reactions were approximately the same as those used in the benzophenone reactions. Twenty-four hundredths of a mole of cyclohexanone, 5 mole per cent of catalyst, and 0.32 moles of Grignard reagent were usually employed. Acetic acid was used to decompose the magnesium alcoholate complex; the product was distilled through a small Podbielniak column. The 1-methyl cyclohexanol-1 was refractionated until it melted at 20-22° C., $n^{20}D = 1.4590$. The cyclohexylidene-cyclohexanone found boiled at 130° at 12 mm. and had a refractive index $n^{20}D = 1.5065$. The portion of the product which distilled at 170° at 12 mm. sometimes crystallized slowly as a result of slight contamination with its dehydration product or with cyclohexylidene-cyclohexanone. When recrystallized from petroleum ether, the melting point of this substance (A) was 74-75° C. The composition of compound A is as follows:

Anal. Calc's for $C_{13}H_{24}O_2$; C, 73.6; H, 11.3; mol. wt., 216.
Found: C, 73.65; H, 11.5; mol. wt., 187.

Zerewitinoff[3] analysis indicates two active hydrogens. The failure of A to react with acetic anhydride in pyridine[4] indicates

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[1]Guyot, Ann. chim., [9] 10, 196 (1918).

[2]Baeyer, Ber., 35, 3016 (1902).

[3]Niederl and Niederl, Micromethods of Quantitative Organic Elementary Analysis. New York: John Wiley and Sons, 1938, pp. 206-13.

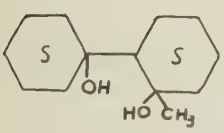
[4]Cooper, Ph. D. Dissertation, University of Chicago, 1937.

that the molecule contains no primary or secondary hydroxyl groups. When A is dehydrated by heating with iodine, an unsaturated compound (B) is obtained (b. p. 132-134° at 22 mm.). The composition of B is:

Anal. Calc'd. for $C_{13}H_{20}$ C, 88.57; H, 11.4.
Found: C, 88.42; H, 11.4.

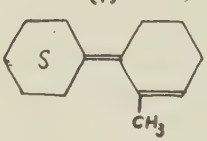
All these properties agree with the structural formulae:

A

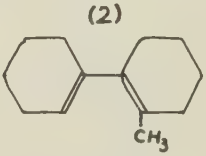


B

(1)



(2)



Since B has an index of refraction of 1.5090, it is probably a mixture of compound B(1) ($n^{20}D$=1.5165)[1] + B(2) (previously unreported) or, less probably, pure B (2).

Reactions of phenyl- and isobutyl-magnesium bromides with cyclohexanone.--The procedure was the same as that used in the reactions between cyclohexanone and methylmagnesium bromide. No cyclohexyl pinacol and no compound A was obtained.

Reaction of methylmagnesium bromide with cyclohexylidene-cyclohexanone.--Cyclohexylidene-cyclohexanone was prepared according to the method of Sen and Neogi[2] by passing dry hydrogen chloride into purified cyclohexanone. It was found necessary to heat the mixture for four hours over dry sodium carbonate to remove all traces of hydrogen chloride. After it had been thus treated, it was distilled from a Claisen flask. The fraction boiling between 128° and 129° at 9 mm. was used for the experiment $n^{20}D$=1.5075.

The action of Grignard reagents on unsaturated hydrocarbons in the presence of metallic halides.--The procedure and apparatus were the same as those used with ketonic compounds.

The reaction of 1-phenyl-3-chloro-propane with methylmagnesium bromide.--Sixteen-hundredths of a mole of 1-phenyl-3-chloro-

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[1] Garland and Reid, J. Am. Chem. Soc., 47, 2333 (1925).

[2] Sen and Neogi, J. Ind. Chem. Soc., 7, 305 (1930).

TABLE 6

EFFECT OF METALLIC HALIDES ON THE REACTION BETWEEN CERTAIN GRIGNARD REAGENTS AND CYCLOHEXANONE

Run	Metallic Halide[a]	Grignard	Special Conditions[b]	Yield (%) 1,2 Addition	Other Prods.
a	None	CH_3MgBr		90	3 of A
b	None	CH_3MgBr	-25°	91	3 of A
7	$CoCl_2$	CH_3MgBr		83	9 of A
9	$CoCl_2$	CH_3MgBr	-6°	58	22 of A
10	$CoCl_2$	CH_3MgBr	-20°	54	33 of A
11	$CoCl_2$	CH_3MgBr	-55°	77	9 of A
3	$CoCl_2$	CH_3MgBr	Grignard added to ketone	..	10 of A
6	$CoCl_2$	CH_3MgBr	Grignard added to ketone	61	25 of cyclohexylidene-cyclohexanone
8	$CoCl_2$	CH_3MgBr	Grignard to ketone, high dilution	68	14 of cyclohexylidene-cyclohexanone
5	$CoCl_2$	CH_3MgBr	Halide suspended in ketone during addit.	71	10 of A

TABLE 6--Continued

Run	Metallic Halide[a]	Grignard	Special Conditions[b]	Yield (%) 1,2 Addition	Yield (%) Other Prods.
4	$CoCl_2$ $FeCl_3$	CH_3MgBr	$FeCl_3$ suspended in ketone, added to CH_3MgBr containing $CoCl_2$	75	9 of A
	CoI_2	CH_3MgBr		80	4 of A
	$FeCl_3$	CH_3MgBr		75	2 of A
	$CoCl_2$	$i\text{-}C_4H_9MgBr$		6	86 of cyclohexanol
	$CoCl_2$	C_6H_5MgBr		Products same as reaction with no added metallic halide	

[a]Five mole per cent of metallic halide (based on amount of Grignard reagent) was usually used.

[b]Ordinarily the ketone was added to a mixture of Grignard reagent and metallic halide at 5° C.

TABLE 7

EFFECT OF METALLIC HALIDES ON THE ACTION OF GRIGNARD REAGENTS ON UNSATURATED COMPOUNDS

Unsaturated Cpd. (in Moles)	Grignard (in Moles)	Metallic Halide (2 to 5 Mole %)	Special Conditions or Reactants	Products
Cyclohexene 0.5	CH_3MgBr 0.61	$CoCl_2$	Refluxed 13 hours Let stand 54 hours	Cyclohexene
Styrene 0.5	CH_3MgBr 0.61	$CoCl_2$	(Refluxed 1 hour, let stand overnight)	Styrene
Styrene 0.5	CH_3MgBr 0.61	Cu_2Cl_2		Styrene
Styrene 0.5	CH_3MgBr 0.61	$FeCl_3$		Styrene
Isoprene 0.11	CH_3MgBr 0.27	$CoCl_2$	CH_3MgBr in Bu_2O	1.6g, b.p. 77-85°[11] 1.0g, b.p. 85-95°[11] 2.8g, b.p. 95-210°[11]
Isoprene 0.11	CH_3MgBr 0.27	$FeCl_3$	CH_3MgBr in Bu_2O	2 g high boiling product
Isoprene 0.11	CH_3MgBr 0.27	Cu_2Cl_2	CH_3MgBr in Bu_2O	1g product

TABLE 7--Continued

Unsaturated Cpd. (in Moles)	Grignard (in Moles)	Metallic Halide (2 to 5 Mole %)	Special Conditions or Reactants	Products
Isoprene 0.51	CH_3MgBr 0.67	$CoCl_2$	(CH_3MgBr in Et_2O)	2g product
Isoprene 0.51	CH_3MgBr 1.22	$CoCl_2$	CH_3MgBr in Bu_2O	1.9g, b.p. 60-82°$_9$ 1.9g, b.p. 90-102$_8$ 1.7g, b.p. 145-195$_8$ 4g of tar
Isoprene 0.3	CH_3MgBr 0.35	$CoCl_2$	(CH_3MgBr in Et_2O) CH_3CH_2Br 0.33 moles	0.6g, b.p. 80-92°$_8$ 3.0g, b.p. 92-102°$_8$ 2.2g, b.p. 102-127°$_9$ 2g of tar
Isoprene 0.15	CH_3MgBr 0.18	None	0.17 moles of CH_3CH_2Br	None
Isoprene 0.15	None	$CoCl_2$	0.17 moles of CH_3CH_2Br	None
Isoprene 0.30	C_6H_5MgBr 0.34	$CoCl_2$		Only diphenyl
Isoprene 0.30	C_6H_5MgBr 0.31	$FeCl_3$		2g, b.p. 80-100°$_{10}$

propane ($n^{20}D$=1.5222) was added to a mixture of 0.24 moles of methylmagnesium bromide and 5 mole per cent of cobaltous chloride at 5°C. The runs were worked up in the usual manner. Halogen titration of the aqueous washings indicated 0.42 moles of soluble halide. This finding is in contrast to the control run (without metallic halide) in which 0.24 moles of soluble halide were found (i.e., there was no soluble halogen increase) and 0.157 moles (98%) of 1-phenyl-3-chloro-propane with an index of refraction $n^{20}D$=1.5221 were recovered. Approximately 5 liters (0.2 moles) of gas were evolved in a reaction where 0.194 moles of 1-phenyl-3-chloro-propane, 0.129 moles of methylmagnesium bromide, and 5 mole per cent of cobaltous chloride were used. The molecular weight of the gas (16.6) indicates that it is methane.[1] The liquid products were distilled at 97 mm. pressure through a 35 cm. column filled with single spiral glass helices. Three fractions were taken:

Fraction	Weight	Boiling Point	$n^{20}D$	% Unsaturation
1	5.7 g.	81-83°	1.5011	75
2	5.0 g.	83-88°	1.5073	85
3	3.2 g.	93-94°	1.5411	90

The residue was transferred to a Claisen flask and redistilled. A fourth fraction (2 grams, b.p. 60-65° at 18 mm.) and a fifth fraction (1 gram, b.p. 180-220° at 18 mm.) were thus obtained. The tarry residue weighed 3 grams. Treatment of fraction 3 with bromine gave a crystalline compound which melted at 65.5-66.5° and was therefore 1,2-dibromo-1-phenyl propane.[3]

Reaction of cinnamyl chloride with methylmagnesium bromide. --In a typical run, freshly distilled cinnamyl chloride[4] (0.13 moles) was slowly added to a mixture of 0.23 moles of methylmagnesium bromide and 5 mole per cent of the particular metallic halide under study. Products were worked up in the usual manner. In all experiments, halogen titration showed that all the halogen in the

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[1] The method of analysis used was that of Kharasch and Lewis, J. Am. Chem. Soc., 64, now in press.

[2] Unsaturation tests were carried out according to the method of Frances, Ind. Eng. Chem., 18, 821 (1926).

[3] Rugheimer, Ann., 172, 131 (1874).

[4] Gilman and Harris, Rec. trav. chim., 50, 1052 (1931).

cinnamyl chloride had been converted to soluble halide. The hydrocarbon product was first distilled. The first fraction was 1-phenylbutylene-1 distilling at 63-64° at 6 mm. Two other cuts were usually made, one at 170-180° at 7 mm., and one at 180-200° at the same pressure. The lower fraction was usually an oil; and the upper one, a mixture of oil and solid. The two were separated by filtration. The filtered oil was then allowed to stand for several days, and finally refiltered. The solid, after all oil had been removed, was crystallized from alcohol. Its melting point was 80-82°. The melting point of dicinnamyl is reported as 81-82°. The tetrabromide of dicinnamyl was prepared by the method of Rupe[1], m.p. 191-193°. On treating the solid with 1,3,5-trinitrobenzene a crystalline addition product melting at 145-146° was obtained. Kuhn[2] reported that dicinnamyl forms such a compound melting at 145.5°. The oil was redistilled and found to have a boiling point of 180-185° at 8 mm. and an index of refraction $n^{20}D=1.5890$. The oil is therefore the 1,4-diphenyl-hexadiene-1,5 ($n^{20}D=1.5885$) identified by Gilman.[3]

Reaction of phenylacetylene bromide with methylmagnesium bromide.--Freshly distilled phenylacetylene bromide[4] (0.097 moles) was slowly added to 0.16 moles of methylmagnesium bromide. After the product had been treated with acetic acid, the aqueous washings were found to contain 0.16 moles of soluble halide. The liquid product distilled at 43-44° at 18 mm. and was therefore phenylacetylene. The yield was 8.8 grams (89 per cent of that calculated). In a second experiment, with 0.09 moles of phenylacetylene bromide and 0.16 moles of Grignard reagent, dry carbon dioxide was run into the cold reaction mixture after it had been refluxed for an hour. When the product was worked up, 7.2 grams (55%) of phenyl propiolic acid melting at 136-137° were obtained, together with 1.9 grams (21%) of phenylacetylene boiling at 140° at 760 mm.

When 5 mole per cent of cobaltous chloride was added to

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[1]Rupe and Bürgin, Ber., 43, 173 (1910).

[2]Kuhn, Helv. Chim. Acta, 11, 132 (1928).

[3]Gilman and Harris, J. Am. Chem. Soc. 54, 2072 (1932).

[4]Straus, Ber., 63, 1880 (1930).

0.16 moles of Grignard reagent and 0.1 mole of phenylacetylene bromide was dropped in, the reaction was quite different from that in the runs without metallic halide. After the reaction mixture had been refluxed and decomposed with acetic acid, it was found by halogen titration to contain 0.281 moles of soluble halide. This finding indicates a 100 per cent reaction. The reaction product, $C_6H_5C{\equiv}CCH_3$, boiled at 75-78° at 18 mm., $n^{20}D$=1.5600. The yield was 7.2 grams or 62 per cent. Four and three-tenths grams of tar were also formed. No diphenyl diacetylene could be isolated.

SUMMARY

1. The effect of some metallic halides on the reactions of Grignard reagents with several types of organic compounds has been studied.

2. It has been shown that magnesium metal, manganous chloride, and cuprous chloride have no effect on the reaction between methylmagnesium bromide and benzophenone. Cobaltous chloride is powerful in effecting the formation of benzopinacol; ferric chloride is intermediate in its effect.

3. With isobutylmagnesium bromide and benzophenone, cobaltous chloride at 5° favors the formation of benzopinacol, although its effect is not nearly as great as in the methylmagnesium bromide-benzophenone reaction. At -40° cobaltous chloride produces a much smaller proportion of benzopinacol. Cobaltous chloride also produces benzopinacol in the phenylmagnesium bromide-benzophenone reaction.

4. No cyclohexyl pinacol was found in the reaction between methylmagnesium bromide and cyclohexanone in the presence of several metallic halides.

5. Methylmagnesium bromide and 1-phenyl-3-chloropropane in the presence of cobaltous chloride from allyl benzene, propenyl benzene, and propyl benzene.

6. Cuprous chloride does not affect the reaction between cinnamyl chloride and methylmagnesium bromide. Ferric chloride, manganous chloride, chromic chloride, nickel chloride, and cobaltous chloride give progressively larger amounts of the coupled products, dicinnamyl and 1,4-diphenyl-hexadiene-1,5.

7. Whereas phenylacetylene bromide normally exchanges its bromine atom for the -MgBr group in the reaction with methylmagnesium bromide, it forms phenylmethyl acetylene in the presence of cobaltous chloride.

8. A mechanism for the reactions is suggested.